

Occupational Risk Factors for Pancreatic Cancer: A Case-Control Study Based on Death Certificates From 24 U.S. States

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Background *The relation between occupational exposure and pancreatic cancer is not well established. A population-based case-control study based on death certificates from 24 U.S. states was conducted to determine if occupations/industries or work-related exposures to solvents were associated with pancreatic cancer death.*

Methods *The cases were 63,097 persons who died from pancreatic cancer occurring in the period 1984–1993. The controls were 252,386 persons who died from causes other than cancer in the same time period.*

Results *Industries associated with significantly increased risk of pancreatic cancer included printing and paper manufacturing; chemical, petroleum, and related processing; transport, communication, and public service; wholesale and retail trades; and medical and other health-related services. Occupations associated with significantly increased risk included managerial, administrative, and other professional occupations; technical occupations; and sales, clerical, and other administrative support occupations. Potential exposures to formaldehyde and other solvents were assessed by using a job exposure matrix developed for this study. Occupational exposure to formaldehyde was associated with a moderately increased risk of pancreatic cancer, with ORs of 1.2, 1.2, 1.4 for subjects with low, medium, and high probabilities of exposure and 1.2, 1.2, and 1.1 for subjects with low, medium, and high intensity of exposure, respectively.*

Conclusions *The findings of this study did not suggest that industrial or occupational exposure is a major contributor to the etiology of pancreatic cancer. Further study may be needed to confirm the positive association between formaldehyde exposure and pancreatic cancer. Am. J. Ind. Med. 36:260–270, 1999. Published 1999 Wiley-Liss, Inc.[†]*

KEY WORDS: *case-control study; formaldehyde; industry; occupation; pancreatic cancer; solvents; job-exposure matrix*

INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer death in the United States. A total of 28,900 cancer deaths were estimated to be due to pancreatic cancer in the U.S. in 1998 [Landis et al., 1998]. Pancreatic cancer mortality rates increased threefold among both white and nonwhites between 1920–1965, with rates declining after 1965 [Pollack and Horm, 1980; Landis et al., 1998]. The etiology of pancreatic cancer has not been established; cigarette smoking is the most well-understood risk factor [IARC,

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1986a]. Epidemiological studies have reported increased risks for those employed in various occupations and industries [Anderson et al., 1996] and for those with exposures to various chemicals, such as pesticides, gasoline, and solvents [Lin and Kessler, 1981; Thomas et al., 1985; Garabrant et al., 1992; Ruder et al., 1994; Neugut et al., 1987; Fryzek et al., 1997], but evidence of occupational effects has been inconsistent across studies. The purpose of this study is to examine the risk of pancreatic cancer by occupation and industry as well as risk among workers exposed to solvents based on death certificate data from 24 states in the U.S.

MATERIALS AND METHODS

The National Cancer Institute, National Institute for Occupational Safety and Health, and the National Center for Health Statistics supported the coding of occupation and industry on death certificates from 24 participating states. The coding of the usual occupation and industry on death certificates was performed according to the classification system designed for the 1980 U.S. census. The International Classification of Disease (ICD, 9th Rev.) was used to code the underlying cause of death. In the period 1984–1993, 63,097 subjects died from pancreatic cancer (ICD 157). Controls were selected from all subjects who died from causes other than cancer in the same time period. For each case, four controls were frequency-matched by state, race, gender, and 5-year age group. Deaths due to pancreatitis and other pancreatic diseases were excluded from the control group. A total of 252,386 controls were selected for analysis.

Overall, 509 occupation codes (OC) and 231 industry codes (IC) were screened in this dataset. For analytic purposes, 3-digit codes were grouped into 16 broad occupational and 20 industrial categories based on similarity of occupational exposures. In addition to usual occupation, the death certificates also provided information on marital status (ever vs. never married), residential status (metropolitan vs. nonmetropolitan), and region of residence (East: Maine, New Hampshire, New Jersey, Rhode Island, Vermont; North-Central: Indiana, Ohio, Wisconsin; South-Central: Kansas, Oklahoma, Missouri, Nebraska; South: Kentucky, Georgia, North Carolina, South Carolina, Tennessee, West Virginia; and West: Colorado, Idaho, Nevada, New Mexico, Utah, and Washington).

To further evaluate the effects of specific exposure to solvents, a job-exposure matrix (JEM) was applied. Industrial hygienists developed JEMs for formaldehyde and 11 chlorinated hydrocarbons (carbon tetrachloride, chloroform, 1,2-dichloroethylene, 1,2-dichloroethane, methyl chloride, methyl chloroform, dichloromethane (methylene chloride), tetrachloroethylene, tetrachloroethane, trichloroethylene, and 1,1,2-trichloroethane), which

have been evaluated as carcinogens in human and animal studies [IARC, 1986b]. In addition, two combination groups of solvents, all chlorinated hydrocarbons and organic solvents, were observed. The indexes of probability and intensity were used to estimate exposures to the solvents under each job title. Both intensity and probability were scored as none, low, medium, and high according to the exposure level by each 3-digit occupation and industry code.

Mortality odds ratios (ORs) and 95% confidence intervals (CIs) were computed to estimate risk for pancreatic cancer death by occupation, industry, and exposure to various solvents using logistic regression procedures. The analyses were performed using Epicure software [Preston and Lubin, 1992]. Pancreatic cancer risk among deceased individuals with specified OC and IC categories (exposed) was compared to the risk among subjects not included in the specified OC and IC categories (unexposed). The risk for each individual solvent was estimated by levels of intensity and probability of exposure (low, medium, and high vs. never exposed to the solvent). Race- and gender-specific mortality ORs were calculated for black women, black men, white women, and white men. The ORs were adjusted for age, marital status, metropolitan, and residential status. No information about cigarette smoking and other lifestyle factors were available for adjustment in the analyses. The overall ORs, collapsing race and gender groups, were further adjusted for race and gender.

RESULTS

Among industry categories, statistically significant small increased risks were associated with printing and paper manufacturing (IC = 160–172) and chemical, petroleum, and related processing (IC = 180–212) among white women and men, with a 20% increase in risk for white women and 10% for white men for both industry categories (Table I). The increased risk associated with printing and paper manufacturing was also observed among black men (OR = 1.2, CI = 0.9–1.8). Significant positive associations with transport, communication, and public service industries (IC = 400–472) were observed in the four gender/race groups, with the risks higher among blacks (women: OR = 1.4, CI = 1.0–2.0; men: OR = 1.2, CI = 1.0–1.3) than whites (women: OR = 1.1, CI = 1.1–1.2; men: OR = 1.1, CI = 1.0–1.1). The risks of pancreatic cancer mortality were also increased among black women (OR = 1.2, CI = 1.0–1.4), white women (OR = 1.3, CI = 1.2–1.4), and white men (OR = 1.2, CI = 1.1–1.2) in the wholesale and retail trade industry, but not among black men. Individuals who worked in the medical and other health-related service industry (IC = 812–841), educational service (IC = 842–862), and social and community services (IC = 870–892) had 10–50% excesses in risk of pancreatic cancer death in the four gender/race groups. No significant excess risks of

TABLE I. Odds Ratios (ORs) * with 95% Confidence Intervals (CIs) for Pancreatic Cancer in Relation to Industry by Race and Gender in 24 US States, 1984–1993

Industry [census codes]	Black females			Black males			White females			White males		
	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI
Agricultural, gardening, forestry, fishing [010–031]	61	0.6	0.4–0.7	304	0.9	0.8–1.0	130	1.0	0.1–0.4	2,470	1.0	0.9–1.0
Mining and quarrying [040–050]	—	—	—	20	0.6	0.4–1.0	25	1.2	0.8–1.9	548	0.8	0.7–0.9
Construction [060]	6	1.2	0.5–3.0	451	1.0	0.9–1.1	95	1.1	0.9–1.4	2,878	0.9	0.9–1.0
Food, beverage, and tobacco industries [100–132]	49	0.7	0.5–1.0	97	0.9	0.7–1.1	313	1.0	0.9–1.1	708	1.1	1.0–1.2
Textile industries [140–152]	72	0.9	0.7–1.2	101	1.1	0.9–1.4	924	1.0	0.9–1.1	643	0.9	0.8–1.0
Printing and paper manufacturing [160–172]	6	0.5	0.2–1.3	43	1.2	0.9–1.8	284	1.2	1.0–1.3	657	1.1	1.0–1.2
Chemical, petroleum, and related processing [180–212]	17	1.2	0.7–2.1	64	1.0	0.7–1.3	226	1.2	1.0–1.4	753	1.1	1.0–1.2
Leather and shoe processing industries [220–222]	1	0.3	—	7	1.4	0.6–3.3	63	0.9	0.7–1.2	436	0.9	0.8–1.0
Timber and furniture industries [230–242]	11	1.0	0.5–2.0	103	0.8	0.6–1.0	72	1.0	0.7–1.3	262	0.9	0.8–1.0
Glass cement and pottery industries [250–262]	7	1.4	0.6–3.3	36	0.9	0.6–1.3	1,144	1.1	1.0–1.2	4,063	1.0	0.9–1.0
Metal and machinery manufacturing [270–392]	75	0.8	0.6–1.0	432	1.0	0.9–1.1	567	1.1	1.0–1.2	2,877	1.0	0.9–1.0
Transport, communication, and public service [400–472]	48	1.4	1.0–2.0	446	1.2	1.0–1.3	2,799	1.1	1.1–1.2	3,451	1.1	1.0–1.1
Wholesale and retail trade [500–691]	195	1.2	1.0–1.4	238	1.0	0.9–1.2	717	1.3	1.2–1.4	914	1.2	1.1–1.2
Banking, insurance, and real estate [700–712]	29	1.1	0.7–1.7	40	0.8	0.6–1.2	1,559	1.1	1.0–1.1	1,375	0.9	0.8–1.0
Personal and repair services [721–791]	860	0.8	0.7–0.9	265	1.0	0.9–1.2	102	1.2	1.0–1.5	169	0.9	0.7–1.0
Art and recreation [800–802]	7	0.9	0.4–2.1	18	0.6	0.4–1.0	102	1.2	1.0–1.5	169	0.9	0.7–1.0
Medical and other health, related services [812–841]	356	1.2	1.0–1.6	113	1.3	1.0–1.6	1,815	1.1	1.0–1.1	665	1.2	1.1–1.4
Educational services [842–862]	342	1.4	1.2–1.6	151	1.3	1.1–1.6	2,094	1.3	1.2–1.4	941	1.2	1.1–1.3
Social and community services [870–892]	76	1.5	1.2–2.0	79	1.1	0.9–1.5	484	1.2	1.1–1.4	669	1.2	1.1–1.4
Government, public administration, and defense [900–932]	91	1.3	1.0–1.6	208	0.9	0.1–0.3	706	1.1	1.0–1.2	2,033	1.1	1.0–1.1
Other industries [951–990]	1,540	0.8	0.7–0.9	244	0.8	0.7–0.9	14,092	0.8	0.7–0.8	855	0.8	0.7–0.8

* ORs adjusted for age, metropolitan status, region of residence, and marital status.

cancer death were associated with other industry groups (Table I).

In the occupational analyses, 30–40% increases in risk were associated with managerial, administrative, and other professional occupations (OC = 003–199) in the four gender/ethnic groups (Table II). Increased risks associated with technical occupations (OC = 203–235), including

biological technicians and medical laboratory-related workers, were observed among black women (OR = 1.5, CI = 1.2–2.0) and black men (OR = 1.4, CI = 1.0–2.2). The excess risks for several hospital or health-related individual occupations raise particular interest under these two white-collar categories. For example, ORs for physician (OC = 084) and dentists (OC = 085) were 1.4 (CI = 1.2–

TABLE II. Odds Ratios (ORs) * with 95% Confidence Intervals (CIs) for Pancreatic Cancer in Relation to Occupation by Race and Gender in 24 US States, 1984–1993

Occupation [census codes]	Black females			Black males			White females			White males		
	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI
Managerial, administrative, and other professional occupations [003–199]	369	1.4	1.2–1.5	258	1.3	1.1–1.5	3,835	1.3	1.2–1.3	5,685	1.3	1.2–1.3
Technical occupations [203–235]	71	1.5	1.2–2.0	26	1.4	1.0–2.2	330	1.0	0.9–1.2	354	1.0	0.9–1.2
Sales, clerical and other administrative support occupations [243–389]	200	1.4	1.2–1.7	204	1.2	1.0–1.4	4,854	1.2	1.2–1.3	3,963	1.0	1.0–1.1
Public sector occupations [403–469]	1,263	1.1	1.0–1.2	504	1.1	1.0–1.2	2,345	1.0	0.9–1.0	1,605	0.9	0.9–1.0
Agriculture, forestry, fishery and hunting [473–499]	62	0.7	0.5–0.9	351	0.9	0.8–1.0	9.1	1.0	0.8–1.2	2,532	1.0	0.9–1.0
Repair and construction-related occupations [503–549]	3	0.7	0.2–2.7	139	1.2	1.0–1.4	35	1.1	0.8–1.6	176	0.9	0.9–1.0
Construction occupations [553–599]	1	0.6	—	227	1.0	0.9–1.2	20	1.2	0.7–2.0	2,218	0.9	0.9–1.0
Mining occupations [613–617]	—	—	—	11	0.5	0.3–0.9		0.9	0.7–1.2	436	0.9	0.8–1.0
Production, precision production, or other public services [633–699]	50	1.2	0.9–1.7	12	1.0	0.8–1.3	398	1.1	1.0–1.2	2,061	1.0	1.0–1.1
Operators and fabricators [703–728]	7	2.0	0.8–5.0	36	0.7	0.5–1.1	35	0.9	0.6–1.3	275	0.9	0.8–1.1
Paper processing [733–739]	12	1.3	0.7–2.6	16	1.3	0.8–2.4	303	0.9	0.9–1.0	252	1.0	0.8–1.1
Textile/shoe processing occupations [743–749]	116	0.9	0.7–1.1	69	0.9	0.7–1.2	634	1.1	1.0–1.2	185	0.8	0.7–1.0
Machinery operators and structural or repair occupations [753–899]	175	1.0	0.8–1.2	1,247	1.0	0.9–1.0	1,292	1.0	0.9–1.1	4,909	0.9	0.8–0.9
Military science occupations [905]	—	—	—	46	1.0	0.7–1.4	11	1.0	0.5–2.0	491	1.0	0.9–1.1
Other occupations [913–917]	1,446	0.8	0.7–0.9	97	0.6	0.5–0.8	13,802	0.8	0.8–0.8	434	0.6	0.6–0.7

* ORs adjusted for age, metropolitan status, region of residence, and marital status.

1.7) and 1.3 (CI = 1.0–1.2), respectively, among white men. ORs for clinical laboratory technicians (OC = 203) were 3.2 (CI = 1.3–7.8) among black women and 1.9 (CI = 0.7–5.1) among black men; OR for licensed practical nurses (OC = 207) was 1.4 (CI = 1.0–1.9) among black women. Among whites, although overall risk for the category of technical occupations was not elevated, increased risks were associated with clinical laboratory technicians (OC = 203) (OR = 1.4, CI = 1.0–2.2), dental hygienists (OC = 204) (OR = 2.4, CI = 1.0–5.4), biological technicians (OC = 223) (OR = 2.3, CI = 1.0–5.1), and chemical technicians (OC = 224) (OR = 4.0, CI = 1.4–11.5) in women and mechanical technicians (OC = 215) (OR = 3.1,

CI = 1.2–8.0) in men. Risk of pancreatic cancer death was also increased among individuals who were employed as sales, clerical, and other administrative support occupations (OC = 243–389) among black women, black men, and white women. Nonsignificant increased risks were observed among blacks who were employed in paper processing occupations (OC = 733–739) and operators and fabricators (OC = 703–728), but the observations were based on a small number of subjects.

To further evaluate the effects of occupational exposure to solvents, JEMs were applied for specific solvents based on the occupation and industry of each study subject. Table III provides ORs for intensity of exposure to 12 solvents, as

TABLE III. Odds Ratios (ORs) * with 95% Confidence Intervals (CIs) for Pancreatic Cancer in Relation to Intensity of Exposure to Solvents by Race and Gender in 24 US States, 1984–1993.

Solvent	Exposure Intensity	Black females			Black males			White females			White males		
		No. of exposed cases	OR	CI	No. of exposed cases	OR	CI	No. of exposed cases	OR	CI	No. of exposed cases	OR	CI
Formaldehyde	Low	3,179	1.0	(0.8–1.4)	2,552	1.1	(0.9–1.4)	23,271	1.3	(1.1–1.5)	20,251	1.2	(1.1–1.4)
	Medium	586	1.1	(0.9–1.5)	767	1.1	(0.9–1.4)	4,822	1.4	(1.2–1.7)	6,649	1.2	(1.1–1.3)
	High	12	1.2	(0.6–2.4)	15	1.0	(0.5–1.7)	92	1.3	(1.0–1.7)	155	1.1	(0.9–1.3)
Carbon tetrachloride	Low	265	0.9	(0.8–1.1)	875	0.9	(0.9–1.0)	727	1.0	(1.0–1.1)	5,471	1.0	(0.9–1.0)
	Medium	30	1.1	(0.8–1.7)	125	0.9	(0.7–1.1)	291	1.0	(0.9–1.1)	1,140	0.9	(0.8–0.9)
	High	87	0.9	(0.7–1.2)	68	1.0	(0.8–1.3)	618	1.1	(1.0–1.2)	413	0.8	(0.8–0.9)
Chloroform	Low	208	1.1	(0.9–1.2)	449	1.1	(0.9–1.2)	632	1.1	(1.0–1.2)	1,770	1.0	(0.9–1.0)
	Medium	54	1.1	(0.8–1.5)	43	0.9	(0.7–1.3)	361	1.1	(1.0–1.3)	422	1.1	(1.0–1.2)
	High	29	0.7	(0.5–1.1)	27	1.2	(0.8–1.9)	153	1.0	(0.9–1.2)	129	0.8	(0.7–1.0)
1,2-Dichloroethylene	Low	316	1.1	(1.0–1.3)	623	1.0	(0.9–1.1)	817	1.0	(0.9–1.1)	1,885	1.0	(0.9–1.0)
	Medium	7	0.8	(0.3–1.8)	7	0.7	(0.3–1.6)	16	0.8	(0.5–1.4)	68	0.9	(0.7–1.1)
	High	29	0.8	(0.5–1.1)	20	0.8	(0.5–1.2)	63	0.8	(0.6–1.1)	118	0.8	(0.7–1.0)
1,2-Dichloroethane	Low	270	1.2	(1.1–1.4)	749	1.0	(0.9–1.1)	899	1.0	(0.9–1.1)	3,106	1.0	(0.9–1.0)
	Medium	22	1.0	(0.6–1.6)	131	1.1	(0.9–1.3)	244	1.0	(0.9–1.1)	1,052	0.9	(0.8–0.9)
	High	27	0.7	(0.5–1.1)	30	1.0	(0.7–1.5)	59	0.8	(0.6–1.1)	59	0.7	(0.5–0.9)
Methyl Chloride	Low	374	1.1	(0.1–1.2)	777	1.0	(0.9–1.1)	1,192	1.0	(1.0–1.1)	2,880	1.0	(0.9–1.0)
	Medium	23	1.1	(0.7–1.8)	90	0.9	(0.7–1.2)	153	1.0	(0.8–1.2)	1,174	1.0	(1.0–1.1)
	High	28	0.7	(0.5–1.0)	79	1.0	(0.8–1.3)	73	0.9	(0.7–1.1)	516	0.8	(0.8–0.9)
Methyl Chloroform	Low	312	1.0	(0.8–1.1)	926	0.9	(0.9–1.0)	1,003	1.1	(1.0–1.2)	5,359	1.0	(0.9–1.0)
	Medium	22	1.1	(0.7–1.7)	101	1.1	(0.9–1.5)	236	1.0	(0.8–1.1)	1,027	1.0	(0.9–1.1)
	High	42	0.8	(0.5–1.1)	83	1.2	(0.9–1.5)	382	1.1	(1.0–1.2)	507	0.9	(0.8–0.9)
Dichloromethane	Low	316	1.0	(0.8–1.1)	949	0.9	(0.9–1.0)	1,114	1.1	(1.0–1.2)	5,968	1.0	(0.9–1.0)
	Medium	39	1.2	(0.8–1.7)	137	1.1	(0.9–1.3)	362	1.0	(0.9–1.1)	1,183	1.0	(0.9–1.0)
	High	4	0.8	(0.3–2.2)	71	1.1	(0.8–1.4)	178	1.3	(1.1–1.6)	434	0.8	(0.7–0.9)
Tetrachloroethylene	Low	212	1.1	(0.9–1.2)	762	1.0	(0.9–1.1)	711	1.1	(1.0–1.2)	3,659	1.0	(0.9–1.0)
	Medium	21	0.9	(0.5–1.5)	166	1.1	(0.9–1.3)	297	1.0	(0.9–1.2)	1,703	0.9	(0.9–1.0)
	High	44	0.8	(0.6–1.2)	78	1.2	(0.9–1.5)	314	1.0	(0.9–1.2)	467	0.9	(0.8–1.0)
Tetrachloroethane	Low	214	1.1	(0.9–1.3)	745	1.0	(0.9–1.1)	752	1.1	(1.0–1.2)	2,740	0.9	(0.9–1.0)
	Medium	18	1.0	(0.6–1.6)	87	1.1	(0.9–1.4)	208	1.0	(0.8–1.1)	578	0.9	(0.8–1.0)
	High	2	0.9	(0.2–4.2)	13	1.0	(0.5–1.8)	18	1.3	(0.8–2.2)	45	0.9	(0.7–1.3)
Trichloroethylene	Low	414	1.1	(1.0–1.3)	841	1.0	(0.9–1.1)	1,363	1.1	(1.0–1.1)	3,652	1.0	(0.9–1.0)
	Medium	34	1.0	(0.7–1.5)	97	1.1	(0.9–1.4)	486	0.9	(0.8–1.0)	910	1.0	(1.0–1.1)
	High	44	0.8	(0.6–1.1)	105	1.1	(0.9–1.4)	387	1.1	(1.0–1.2)	735	0.9	(0.8–0.9)
1,1,2-Trichloroethane	Low	28	0.9	(0.6–1.4)	429	0.9	(0.8–1.0)	352	1.0	(0.9–1.2)	2,094	0.9	(0.9–1.0)
	Medium	20	1.2	(0.7–1.9)	87	1.0	(0.8–1.3)	186	0.9	(0.8–1.1)	901	1.0	(0.9–1.0)
	High	13	1.0	(0.6–1.9)	54	1.1	(0.8–1.5)	139	0.9	(0.8–1.1)	417	0.9	(0.8–1.0)
Chlorinated hydrocarbons	Low	442	1.0	(0.9–1.1)	1,224	1.0	(0.9–1.0)	1,220	1.0	(0.9–1.1)	6,773	1.0	(0.9–1.0)
	Medium	87	1.1	(0.9–1.5)	145	1.0	(0.9–1.2)	855	1.0	(0.9–1.1)	1,623	1.0	(0.9–1.0)
	High	47	0.8	(0.6–1.1)	113	1.1	(0.9–1.3)	415	1.1	(1.0–1.2)	790	0.8	(0.8–0.9)
Organic solvents	Low	400	1.0	(0.9–1.2)	1,030	1.0	(0.9–1.1)	1,055	1.0	(1.0–1.1)	5,791	1.0	(0.9–1.0)
	Medium	68	1.1	(0.8–1.5)	149	1.0	(0.8–1.1)	480	1.1	(1.0–1.2)	1,558	1.0	(0.9–1.1)
	High	45	0.8	(0.6–1.1)	103	1.1	(0.8–1.3)	376	1.1	(1.0–1.2)	794	0.8	(0.8–0.9)

* ORs adjusted for age, metropolitan status, region of residence, and marital status.

TABLE IV. Odds Ratios (ORs) * with 95% Confidence Intervals (CIs) for Pancreatic Cancer in Relation to Probability of Exposure to Solvents by Race and Gender in 24 US States, 1984–1993.

Solvent	Probability of exposure	Black females			Black males			White females			White males		
		No. of exposed cases	OR	CI	No. of exposed cases	OR	CI	No. of exposed cases	OR	CI	No. of exposed cases	OR	CI
Formaldehyde	Low	3,253	1.0	(0.8–1.4)	2,792	1.2	(0.9–1.4)	24,140	1.3	(1.1–1.6)	22,117	1.2	(1.1–1.4)
	Medium	475	1.1	(0.9–1.5)	535	1.0	(0.8–1.3)	3,562	1.4	(1.2–1.7)	4,872	1.2	(1.1–1.3)
	High	49	1.3	(0.9–2.0)	7	0.8	(0.3–1.8)	483	1.5	(1.3–1.9)	66	1.2	(0.9–1.6)
Carbon tetrachloride	Low	272	0.9	(0.8–1.1)	666	0.9	(0.8–1.0)	755	1.1	(1.1–1.2)	4,099	0.9	(0.9–1.0)
	Medium	32	0.8	(0.5–1.1)	14	0.6	(0.3–1.1)	90	0.8	(0.7–1.1)	130	0.8	(0.7–1.0)
	High	0	—	—	13	1.9	(1.0–3.7)	1	0.6	—	139	1.2	(1.0–1.4)
Chloroform	Low	162	1.0	(0.9–1.2)	302	1.1	(0.9–1.2)	342	1.1	(1.0–1.2)	817	0.9	(0.8–1.0)
	Medium	40	0.9	(0.7–1.3)	19	0.9	(0.6–1.5)	94	0.9	(0.7–1.1)	212	1.3	(1.1–1.5)
	High	43	1.1	(0.8–1.5)	9	1.6	(0.7–3.5)	258	1.2	(1.0–1.4)	54	1.0	(0.7–1.3)
1,2-Dichloroethylene	Low	295	1.1	(1.0–1.3)	308	1.0	(0.9–1.2)	576	1.0	(0.9–1.1)	745	0.9	(0.8–1.0)
	Medium	25	0.7	(0.5–1.1)	5	0.5	(0.2–1.3)	36	0.7	(0.5–1.0)	25	0.8	(0.5–1.2)
	High	0	—	—	0	—	—	0	—	—	0	—	—
1,2-Dichloroethane	Low	220	1.2	(1.0–1.4)	350	1.0	(0.9–1.1)	558	1.0	(0.9–1.1)	1,308	0.9	(0.8–0.9)
	Medium	29	0.8	(0.5–1.1)	17	1.1	(0.7–1.9)	55	0.8	(0.6–1.0)	71	0.9	(0.7–1.2)
	High	0	—	—	0	—	—	8	2.1	(0.9–5.0)	16	1.6	(0.9–2.8)
Methyl Chloride	Low	345	1.1	(1.0–1.3)	386	1.0	(0.9–1.1)	847	1.0	(1.0–1.1)	1,601	0.9	(0.9–1.0)
	Medium	31	0.8	(0.6–1.2)	13	0.7	(0.4–1.3)	81	0.8	(0.7–1.1)	219	1.1	(0.9–1.2)
	High	0	—	—	8	3.3	(1.3–8.6)	0	—	—	40	1.0	(0.7–1.4)
Methyl Chloroform	Low	274	0.9	(0.8–1.1)	673	0.9	(0.9–1.1)	762	1.1	(1.1–1.2)	3,943	0.9	(0.9–1.0)
	Medium	25	0.7	(0.5–1.1)	5	0.5	(0.2–1.3)	36	0.7	(0.4–0.9)	47	1.0	(0.7–1.3)
	High	4	1.2	(0.4–3.7)	8	2.9	(1.2–7.5)	41	1.0	(0.7–1.4)	48	0.9	(0.7–1.3)
Dichloromethane	Low	272	0.9	(0.8–1.1)	667	0.9	(0.9–1.0)	784	1.2	(1.1–1.3)	4,160	1.0	(0.9–1.0)
	Medium	6	2.0	(0.8–5.4)	28	0.9	(0.6–1.3)	28	0.9	(0.6–1.3)	295	0.9	(0.8–1.0)
	High	7	1.5	(0.6–3.5)	10	2.2	(1.0–4.8)	53	1.0	(0.8–1.4)	79	1.0	(0.8–1.3)
Tetrachloroethylene	Low	170	1.1	(0.9–1.3)	3,70	1.0	(0.9–1.2)	448	1.2	(1.0–1.3)	1,766	0.9	(0.9–1.0)
	Medium	0	—	—	0	—	—	2	0.9	(0.2–4.1)	30	0.9	(0.6–1.4)
	High	29	0.7	(0.5–1.1)	42	1.0	(0.7–1.4)	78	0.8	(0.6–1.1)	374	0.9	(0.8–1.0)
Tetrachloroethane	Low	161	1.0	(0.9–1.3)	328	1.0	(0.9–1.2)	271	1.1	(0.9–1.2)	1,049	0.9	(0.8–0.9)
	Medium	1	2.2	(0.2–24.3)	1	1.2	(0.1–11.9)	7	0.7	(0.3–1.5)	31	1.1	(0.8–1.7)
	High	0	—	—	0	—	—	8	2.1	(0.9–5.0)	16	1.6	(0.8–2.8)
Trichloroethylene	Low	304	1.1	(1.0–1.3)	388	1.1	(0.9–1.2)	768	1.0	(1.0–1.1)	1,620	0.9	(0.9–1.0)
	Medium	20	2.3	(1.3–4.0)	17	1.1	(0.7–2.0)	87	1.2	(0.9–1.5)	264	1.3	(1.1–1.5)
	High	68	0.9	(0.7–1.2)	14	0.9	(0.5–1.7)	301	1.1	(1.0–1.3)	84	1.0	(0.8–1.2)
1,1,2-Trichloroethane	Low	2	1.1	(0.2–5.4)	22	0.8	(0.5–1.2)	23	1.1	(0.7–1.8)	377	0.9	(0.8–1.0)
	Medium	0	—	—	0	—	—	2	0.9	(0.2–4.1)	28	1.0	(0.6–1.5)
	High	4	1.2	(0.4–3.8)	8	3.0	(1.2–7.6)	41	1.0	(0.7–1.4)	48	0.9	(0.7–1.3)
Chlorinated hydrocarbons	Low	363	1.0	(0.9–1.1)	703	1.0	(0.9–1.1)	843	1.0	(1.0–1.1)	4,258	1.0	(0.9–1.0)
	Medium	23	2.4	(1.4–4.0)	36	1.0	(0.7–1.5)	109	1.1	(0.9–1.4)	467	1.1	(1.0–1.3)
	High	72	0.9	(0.7–1.2)	26	0.9	(0.6–1.4)	343	1.1	(1.0–1.2)	260	1.0	(0.9–1.2)
Organic solvents	Low	367	1.0	(0.9–1.1)	705	1.0	(0.9–1.1)	847	1.0	(1.0–1.1)	4,273	1.0	(0.9–1.0)
	Medium	23	2.3	(1.4–3.9)	36	1.0	(0.7–1.5)	108	1.1	(0.9–1.4)	450	1.1	(1.0–1.3)
	High	72	0.9	(0.7–1.2)	26	0.9	(0.6–1.4)	344	1.1	(1.0–1.2)	277	1.0	(0.9–1.2)

* ORs adjusted for age, metropolitan status, region of residence, and marital status.

well as for overall chlorinated hydrocarbons and organic solvents by race and gender. Statistically significant increased risk of pancreatic cancer death was associated with exposure to formaldehyde among whites, with ORs of 1.3, 1.4, and 1.3 among white women; and, 1.2, 1.2, and 1.1 among white men in low, medium, and high categories, respectively. Slightly increased risk was also associated with high exposures to dichloromethane (OR = 1.3, CI = 1.1–1.6) and tetrachloroethane (OR = 1.3, CI = 0.8–2.2) among white women. No positive associations were found with intensity of exposure to other individual solvents or to chlorinated hydrocarbons or organic solvents as a group for any gender/race group.

Risk patterns by probability of exposure were stronger than those observed with intensity of exposures. As shown in Table IV, the increased risks were associated with high probability of occupational exposure to formaldehyde among black women, white women, and white men (ORs were 1.0, 1.1, and 1.3 for black women; 1.3, 1.4, and 1.5 for white women; and 1.2, 1.2, and 1.2 for white men in the low, medium, and high categories of probability, respectively).

Increased risks were associated with high probability of exposure to dichloroethane for white women (OR = 2.1, CI = 0.9–5.0) and white men (OR = 1.6, CI = 0.9–2.8) and to tetrachloroethane for white women (OR = 2.1, CI = 0.9–5.0) and white men (OR = 1.6, CI = 0.8–2.8). Increased risks were also associated with high probability of exposure to dichloromethane for black women (OR = 1.5, CI = 0.6–3.5) and black men (OR = 2.2, CI = 1.0–4.8) and to methyl chloride for black women (OR = 1.2, CI = 0.4–3.7) and black men (OR = 2.9, CI = 1.2–7.5). High risks were associated with high probability of exposure to carbon tetrachloride for black men (OR = 1.9, CI = 1.0–3.7) and white men (OR = 1.2, CI = 1.0–1.4). Risks associated with other solvents were not consistent across gender or race groups. Risks associated with some solvents were increased only among blacks. For example, among black women a

slightly increased risk was associated with probability of high exposure to methyl chloroform, dichloromethane, and with a medium probability of exposure to dichloromethane, tetrachloroethane, trichloroethylene, all chlorinated hydrocarbons (OR = 2.4, CI = 1.4–4.0), and all organic solvents combined (OR = 2.3, CI = 1.4–3.9). But the twofold excesses in risk associated with exposures to dichloromethane and tetrachloroethane were based on a small number of subjects and were not statistically significant. ORs associated with a medium probability of exposure to trichloroethylene, overall chlorinated hydrocarbons, and overall organic solvents were statistically significant. Among black men, increased risk was associated with a high probability of exposure to carbon tetrachloride, chloroform, methyl chloride, methyl chloroform, methylene chloride, and 1,1,2-trichloroethane. No positive associations, however, were found with overall hydrocarbons and overall organic solvents. A few solvents were linked to increased risk among whites, such as high levels of carbon tetrachloride, chloroform, 1,2-dichloroethane, tetrachloroethane, and medium levels of chloroform, and trichloroethylene.

The combined effects of formaldehyde by intensity and probability of exposure are shown in Table V. The overall ORs for all gender and racial groups combined were 1.2 (CI = 1.1–1.3), 1.2 (CI = 1.1–1.3), and 1.1 (CI = 1.0–1.3) among those exposed to the low, medium, and high intensity categories, respectively. The ORs were 1.2 (CI = 1.1–1.3), 1.2 (CI = 1.1–1.3), and 1.4 (CI = 1.2–1.6) among those who had low, medium, and high probabilities of exposure (Table V), respectively. Although the OR was 1.4 (CI = 1.0–1.8) among workers with both high level of intensity and high probability of exposure to formaldehyde, the dose–response gradient with intensity of exposure was not apparent. In contrast, the dose–response relationships by probability of exposure were consistent for each level of exposure intensity. The joint effects of intensity and

TABLE V. Odds ratios (ORs)* and 95% confidence interval (CIs) for pancreatic cancer in relation to formaldehyde by intensity and probability of exposure in 24 US States, 1984–1993

Intensity	Probability							
	Low		Medium		High		All levels	
	No. of exposed cases	OR(95% CI)	No. of exposed cases	OR(95% CI)	No. of exposed cases	OR(95% CI)	No. of exposed cases	OR(95% CI)
Low	48,942	1.2(1.1–1.3)	308	1.2(1.1–1.4)	3	2.8(0.7–1.8)	49,253	1.2(1.1–1.3)
Medium	3,189	1.2(1.1–1.3)	9,089	1.2(1.1–1.3)	546	1.4(1.2–1.6)	12,824	1.2(1.1–1.3)
High	171	1.0(0.9–1.3)	47	1.2(0.8–1.6)	56	1.4(1.0–1.8)	274	1.1(1.0–1.3)
All levels	52,302	1.2(1.1–1.3)	9,444	1.2(1.1–1.3)	605	1.4(1.2–1.6)	—	—

* ORs adjusted for age, sex, race metropolitan status, region of residence, and marital status.

probability of exposure to other solvents were also examined. No interactive effects were found among workers who had both high intensity and high probability of exposure to other individual solvents, as well as to overall chlorinated hydrocarbons and overall organic solvents (data not shown).

DISCUSSION

This case-control study of pancreatic cancer was based on death certificates from 24 U.S. states. Findings from this study confirmed some results from previous epidemiological studies of occupational pancreatic cancer. Our findings further suggest that exposure to formaldehyde and several other solvents may increase the risk of death from pancreatic cancer.

The positive association between probability of occupational exposure to formaldehyde and pancreatic cancer in our study is new. Formaldehyde has been classified as a probable human carcinogen based on animal data and on epidemiologic studies that observed associations with cancers of the nasopharynx, oropharynx, and larynx [Hayes et al., 1986; Vaughan et al., 1986; Blair et al., 1986, 1987; Roush et al., 1987; Wortley et al., 1992; IARC, 1995]. Formaldehyde has also been linked to cancers of the lung, colon, brain, and prostate, and leukemia [Blair et al., 1985b, 1990], but no evidence showed that formaldehyde increased risk of pancreatic cancer in human studies. One mortality study in the U.S. reported a nonsignificant increased risk (PMR = 119 for whites and 167 for nonwhites) among embalmers and funeral directors [Hayes et al., 1990], suggesting a possible association between formaldehyde and pancreatic cancer risk. In our study, the risk of pancreatic cancer increased with increasing probability of exposure to formaldehyde, although the dose-response trend was not consistent for intensity of the exposure.

Besides its wide use in the production of resins with urea, phenol, and melamine and as an intermediate for synthesizing other industrial chemical compounds related to the manufacture of polyurethane and polyester plastics, synthetic resin coatings, synthetic lubricating oils, and plasticizers, formaldehyde is also widely used for preservation and disinfection. Many health-related workers may be exposed to this chemical [IARC, 1995]. In our study, major contributors (over 80%) to the high probability and intensity of exposure to formaldehyde were hospital-related occupations and industries. Experimental studies have not found clear mechanisms of its carcinogenicity to humans, although it has been concluded as a "probable" carcinogen by the IARC working group [1995].

Reports of associations between risk of pancreatic cancer and exposure to other solvents have been inconsistent. In our study, increased risks were associated with occupational exposures to dichloromethane, dichloro-

ethane, and tetrachloroethane. The excesses were also related to occupational exposures to chloroform, methyl chloride, trichloroethylene, dichloromethane, and carbon tetrachloride, but results were not consistent by gender and race. No dose-response relationships were observed for exposures to these solvents. The mechanisms of pancreatic carcinogenesis for these solvents have not been established. A cancer mortality study among chemists suggested that chemical agents may induce pancreatic cancer in the late 60s [Li et al., 1969]. In a cohort study in Finland, an increased risk of pancreatic cancer was found among workers occupationally exposed to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane [Anttila et al., 1995]. A case-control study nested in a cohort of chemical manufacturing workers reported a 7.4-fold excess pancreatic cancer risk among workers exposed to DDT, a compound chemically similar to trichloroethane [Garabrant et al., 1992]. Although dichloromethane has been linked to risk of pancreatic cancer, there is still no convincing evidence of the association. Two U.S. mortality cohort studies, by Ott et al. [1985] and Hearne et al. [1987, 1990], reported a nonsignificant excess in pancreatic cancer mortality among subjects exposed to dichloromethane, but no dose-response effect was observed for either concentration of exposure or latency since first exposure. One mortality study in chlorohydrin production workers, who produced dichloromethane, observed a very high excess of deaths due to pancreatic and lymphopoietic cancers. The risks increased with increasing years of employment in this work unit [Benson and Teta, 1993]. A nationwide case-control study in Finland indicated an increased risk among workers exposed to solvents, including aliphatic and aromatic hydrocarbons, but not for chlorinated hydrocarbons [Kauppinen et al., 1995].

Findings for occupation and industry groups in our study indicated that elevated risks of pancreatic cancer were associated with employment in the following industries: printing and paper manufacturing; chemical, petroleum, and related processing; and transport, communication, and public service. In addition, excess risk of pancreatic cancer in our study was also observed among workers involved in medical and other health-related services, industries, and technical occupations, including clinical laboratory technicians, dental hygienists, nurses, and biological and chemical technicians. Although smoking and other lifestyle factors may also be responsible for the excess risk experienced by workers in these occupations and industries, formaldehyde and other solvents may play a role in the development of pancreatic cancer.

The excess risk for workers in solvent-related occupations and industries has also been reported in previous epidemiological studies, although the findings have not been consistent. Pietri and Clavel [1991] and Wen et al. [1985] reported an increased risk for pancreatic cancer among

workers employed in chemical petroleum processing. However, studies by Falk et al. [1990] and Partanen et al. [1994] failed to demonstrate the excess risk for chemical processing branches. Excess risk for pancreatic cancer was observed for vehicle drivers and railroad workers [Viadana et al., 1976; Mallin et al., 1989; Falk et al., 1990; Partanen et al., 1994], but no association between exposure to diesel exhaust and pancreatic cancer was found in a case-control study in Finland [Kauppinen et al., 1995]. Hansen [1989] reported a twofold excess in mortality of pancreatic cancer in an auto mechanics cohort study. Lin and Kessler [1981] also found an excess risk among those who worked as dry cleaners, service station workers, and garagemen. An occupational mortality study in Washington State also indicated that chemists, chemical engineers, and chemical company workers have increased PMRs for pancreatic cancer [Milham, 1997]. In addition, the increased risks were also associated with the following industries/occupations in other studies: metal manufacture [Milham, 1976; Maruchi et al., 1979; Vena et al., 1985; Silverstein et al., 1988; Mallin et al., 1989; Siemiatycki et al., 1991; Ji et al., 1999]; paper production, printing, and paint industries [Williams et al., 1977; Pickle and Gottlieb, 1980; Falk et al., 1990; Partanen et al., 1994]; and leather industry and leather processing [Zoloth et al., 1986; Pietri and Clavel, 1991; Mikoczy et al., 1994]. Exposures to solvents may be the most likely explanation for the excesses, even though often the specific solvents have not been identified.

Our study has several limitations. First, death certificates may lack accurate occupational information. The most recent occupation and type of industry held by the decedent may be reported on death certificates, although "usual" occupation and industry were requested. This may increase the chance of misclassification of exposure. Moreover, no information about duration of employment and other occupations was recorded. Thus, the exposure assessment based on usual occupation and type of industry may not accurately reflect the exposures related to the cause of death. Second, misdiagnosis of pancreatic cancer was also possible, although since pancreatic cancer is a rapidly fatal malignancy, it is recorded on the death certificate with a high level of diagnostic accuracy [Percy et al., 1981], minimizing diagnostic bias. Third, studies based on death certificates often lack information regarding confounders. No information about cigarette smoking, socioeconomic status, and other lifestyle factors was available in this death certificate-based case-control study; however, lack of adjustment for these factors is unlikely to seriously distort the results in occupational risk estimation [Blair et al., 1985a; Siemiatycki et al., 1988].

In addition, since both "blue-collar" workers (e.g., workers employed in printing and paper manufacturing; chemical, petroleum and related processing industries; and

paper processing occupations) and "white-collar" workers (e.g., workers employed in medical and other health-related services; educational service; social and community services; managerial, administrative, and other professional occupations; and technical occupations) had excess deaths due to pancreatic cancer, the risks of "blue-collar" workers might be possibly attenuated toward null. We did analyses for those "blue-collar" workers, excluding all "white-collar" workers; ORs were not raised significantly. On the other hand, our further analyses of solvents by JEMs of formaldehyde and other chlorinated solvents could reduce this bias.

In summary, our investigation does not indicate that occupational exposure is a major contributor to the etiology of pancreatic cancer, although a few associations warrant further evaluation. Interpretation of the results is difficult due to the limitations in exposure assessment, which would tend to dilute the ORs. Some of these associations were based on small numbers of exposed workers and may be due to chance. Among the solvents, the most consistent association was found for workers exposed to formaldehyde, but investigations are needed to confirm this association. The potential associations with other individual solvents, such as dichloroethylene, dichloromethane, and trichloroethane, may also warrant further study.

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